PATENT COOPERATION TREATY

TRANSLATION

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

	Date of mailing *(day/month/year)*
Applicant's or agent's file reference YCT-1029	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2005/006320	31.03.2005	31.03.2004

International Patent Classification (IPC) or both national classification and IPC

Applicant
TWO CELLS CO. LTD.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☒ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☒ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/JP	Authorized officer
Facsimile No.	Telephone No.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2005/006320

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rule 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☐ in computer readable form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2005/006320

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 9-16

because:

☒ the said international application, or the said claims Nos. 9-16 relate to the following subject matter which does not require an international preliminary examination (*specify*):

The inventions of claims 9-16 concern a treatment of the human body by therapy.

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____ are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 9-16

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2005/006320

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	7	YES
	Claims	1-6, 8	NO
Inventive step (IS)	Claims		YES
	Claims	1-8	NO
Industrial applicability (IA)	Claims	1-8	YES
	Claims		NO

2. Citations and explanations:

Document 1: JP 2000-501966 A
& WO 97/22308 A
& US 6132214 A1
& EP 898975 A
Document 2: JP 2003-325657 A
& WO 03/94987 A
Document 3: JP 2003-111831
Document 4: ANTONELLA Puglianiello, Expression and role of PDGF-BB and PDGFR-β during testis morphogenesis in the mouse embryo, Journal of Cell Science, 2003, Vol. 117, No. 7, p. 1151-1160
Document 5: YING Zhuo, A novel murine PDGF-D spicing variant results in significant differences in peptide expression and function, Biochemical and Biophysical Research Communications, 2003, Vol. 308, p. 126-132
Document 6: Hajime OGUSHI, Kanyokei Kansaibo o Riyo shita Kotsukansetsu Shikkan Chiryo, Experimental Medicine, 2003, Vol. 21, No. 8, p. 161-165
Document 7: Tetsuro SHINGO, No Shinkei Shikkan ni Taisuru Saibo Ishoku Ryoho, Experimental Medicine, 2003, Vol. 21, No. 8, p. 140-147
Document 8: Satoshi INIWA, Kyoketusei Shinzobyo · Kyoketsu Kashi e no Kekkan Saisei o Mokuteki to shita Saibo Chiryo, Experimental Medicine, 2003, Vol. 21, No. 8, p. 154-160

[1] Based on the description in document 1 cited in the international search report, the inventions of claims 1-6 and 8 lack novelty and an inventive step.

More specifically, document 1 describes a medical implant containing an active substance having the property of bone induction as a biologically active substance, and describes EGF, FGF, PDGF, IGF, and the like as physiologically active substances that convert adjacent cells into mesencymal stem cells and stimulate bone formation. Document 1 also describes the use of this implant for deficiency of periodontal and jaw bone.

Document 1 does not state that this physiologically active substance is a factor that accelerates the migration of mesenchymal stem cells or that it promotes the migration of mesenchymal stem cells to damaged tissue and the accumulation thereof therein and/or suppresses the diffusion of mesencymal stem cells away from damaged tissue, but as a transplantation material that contains EGF, FGF, PDGF, IGF and the like and is used for a deficiency of the periodontal or jaw bone, the invention described in document 1 is indistinguishable from the inventions of this application.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2005/006320

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claim 1 is an invention concerning a "drug or transplant material that promotes the migration of mesenchymal stem cells to damaged tissue and the accumulation thereof therein and/or suppresses the diffusion of mesenchymal stem cells away from damaged tissue," and the inventions of claims 2-5 concern a drug or transplant material that promotes the migration of mesenchymal stem cells to damaged tissue and the accumulation thereof therein and/or suppresses the diffusion of mesenchymal stem cells away from damaged tissue having as its active ingredient a factor defined by the desirable property of "accelerating the migration capability of mesenchymal stem cells." The inventions of claims 1-5, therefore, include all factors that have such a property, but this authority finds that only a small part of the claimed factors are supported by the DESCRIPTION in the sense of PCT Article 6 or fully disclosed in the sense of PCT Article 5.

In addition, in light of the level of technical common knowledge at the time this application was filed, the expression "factor that accelerates the migration capability of mesenchymal stem cells" cannot specify the scope of factors having such a property, and therefor the inventions of claims 1-5 do not satisfy the requirement for clarity in accordance with PCT Article 6.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box V.

[2] Based on the descriptions in documents 2 and 3 cited in the international search report, the inventions of claims 1-4, 6, and 8 lack novelty and an inventive step.

See [1] above.

More specifically, document 2 describes a material for the formation of joint cartilage wherein IGF, PDGF, FGF and the like are carried therein, and document 3 describes a bone and cartilage transplant material for filling in an area lacking bone and cartilage wherein bone marrow cells are embedded therein and formed into a single body with a gel. Document 3 also states that FGF, IGF, and PDGF can be made into a composite with this transplant material.

[3] Based on the descriptions in documents 4 and 5 cited in the international search report, the inventions of claims 1-3 and 6 lack novelty and an inventive step.

More specifically, documents 4 and 5 state that PDGF is a chemotaxic substance that is involved in the migration and growth of mesenchymal progenitor cells, and that the expression and activity of PDGF are important in wound healing and the like.

[4] Based on the descriptions in documents 1-8 cited in the international search report, the inventions of claims 1-8 lack an inventive step.

Documents 4 and 5 do not describe making PDGF into a transplant material, using a drug or transplant material containing PDGF in regenerative medicine for tissue and the like that has been damaged by rheumatoid arthritis, fracture, deficiency of periodontal and jaw bone, cerebral infarction, myocardial infarction or ischemia of the lower extremities, and administering that drug or transplantation material concurrently with, consecutively with, or separate from mesenchymal stem cells.

However, this authority finds that documents 1-3 describe the inclusion of PDGF in a transplantation material, and the use of PDGF together with bone marrow cells, including mesenchymal stem cells, and documents 6-8 state that mesencymal stem cells have the capability to differentiate into osteoblasts and cartilage cells, neurons, muscle cells, and the like, and that mesenchymal stem cells can be formed into a transplant material used in regenerative medicine and used for the treatment of bone diseases such as rheumatoid arthritis and the like, and diseases such as myocardial infarction and ischemia of the lower extremities.

This being the case, this authority finds that persons skilled in the art can easily conceive of making PDGF into a transplant material, using a drug or transplant material containing PDGF in regenerative medicine for tissue and the like that has been damaged by rheumatoid arthritis, fracture, deficiency of periodontal and jaw bone, cerebral infarction, myocardial infarction or ischemia of the lower extremities, and using the same together with mesenchymal stem cells.

PATENT COOPERATION TREATY

TRANSLATION

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

	Date of mailing *(day/month/year)*
Applicant's or agent's file reference YCT-1029	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2005/006320	31.03.2005	31.03.2004

International Patent Classification (IPC) or both national classification and IPC

Applicant
TWO CELLS CO. LTD.

1. This opinion contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/JP	Authorized officer
Facsimile No.	Telephone No.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2005/006320

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rule 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☐ in computer readable form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2005/006320

Box No. III **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 9-16

because:

☒ the said international application, or the said claims Nos. 9-16 relate to the following subject matter which does not require an international preliminary examination (*specify*):

The inventions of claims 9-16 concern a treatment of the human body by therapy.

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____ are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 9-16

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2005/006320

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	7	YES
	Claims	1-6, 8	NO
Inventive step (IS)	Claims		YES
	Claims	1-8	NO
Industrial applicability (IA)	Claims	1-8	YES
	Claims		NO

2. Citations and explanations:

Document 1: JP 2000-501966 A
& WO 97/22308 A
& US 6132214 A1
& EP 898975 A
Document 2: JP 2003-325657 A
& WO 03/94987 A
Document 3: JP 2003-111831
Document 4: ANTONELLA Puglianiello, Expression and role of PDGF-BB and PDGFR-β during testis morphogenesis in the mouse embryo, Journal of Cell Science, 2003, Vol. 117, No. 7, p. 1151-1160
Document 5: YING Zhuo, A novel murine PDGF-D spicing variant results in significant differences in peptide expression and function, Biochemical and Biophysical Research Communications, 2003, Vol. 308, p. 126-132
Document 6: Hajime OGUSHI, Kanyokei Kansaibo o Riyo shita Kotsukansetsu Shikkan Chiryo, Experimental Medicine, 2003, Vol. 21, No. 8, p. 161-165
Document 7: Tetsuro SHINGO, No Shinkei Shikkan ni Taisuru Saibo Ishoku Ryoho, Experimental Medicine, 2003, Vol. 21, No. 8, p. 140-147
Document 8: Satoshi INIWA, Kyoketusei Shinzobyo · Kyoketsu Kashi e no Kekkan Saisei o Mokuteki to shita Saibo Chiryo, Experimental Medicine, 2003, Vol. 21, No. 8, p. 154-160

[1] Based on the description in document 1 cited in the international search report, the inventions of claims 1-6 and 8 lack novelty and an inventive step.

More specifically, document 1 describes a medical implant containing an active substance having the property of bone induction as a biologically active substance, and describes EGF, FGF, PDGF, IGF, and the like as physiologically active substances that convert adjacent cells into mesencymal stem cells and stimulate bone formation. Document 1 also describes the use of this implant for deficiency of periodontal and jaw bone.

Document 1 does not state that this physiologically active substance is a factor that accelerates the migration of mesenchymal stem cells or that it promotes the migration of mesenchymal stem cells to damaged tissue and the accumulation thereof therein and/or suppresses the diffusion of mesencymal stem cells away from damaged tissue, but as a transplantation material that contains EGF, FGF, PDGF, IGF and the like and is used for a deficiency of the periodontal or jaw bone, the invention described in document 1 is indistinguishable from the inventions of this application.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2005/006320

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claim 1 is an invention concerning a "drug or transplant material that promotes the migration of mesenchymal stem cells to damaged tissue and the accumulation thereof therein and/or suppresses the diffusion of mesenchymal stem cells away from damaged tissue," and the inventions of claims 2-5 concern a drug or transplant material that promotes the migration of mesenchymal stem cells to damaged tissue and the accumulation thereof therein and/or suppresses the diffusion of mesenchymal stem cells away from damaged tissue having as its active ingredient a factor defined by the desirable property of "accelerating the migration capability of mesenchymal stem cells." The inventions of claims 1-5, therefore, include all factors that have such a property, but this authority finds that only a small part of the claimed factors are supported by the DESCRIPTION in the sense of PCT Article 6 or fully disclosed in the sense of PCT Article 5.

In addition, in light of the level of technical common knowledge at the time this application was filed, the expression "factor that accelerates the migration capability of mesenchymal stem cells" cannot specify the scope of factors having such a property, and therefor the inventions of claims 1-5 do not satisfy the requirement for clarity in accordance with PCT Article 6.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box V.

[2] Based on the descriptions in documents 2 and 3 cited in the international search report, the inventions of claims 1-4, 6, and 8 lack novelty and an inventive step.

See [1] above.

More specifically, document 2 describes a material for the formation of joint cartilage wherein IGF, PDGF, FGF and the like are carried therein, and document 3 describes a bone and cartilage transplant material for filling in an area lacking bone and cartilage wherein bone marrow cells are embedded therein and formed into a single body with a gel. Document 3 also states that FGF, IGF, and PDGF can be made into a composite with this transplant material.

[3] Based on the descriptions in documents 4 and 5 cited in the international search report, the inventions of claims 1-3 and 6 lack novelty and an inventive step.

More specifically, documents 4 and 5 state that PDGF is a chemotaxic substance that is involved in the migration and growth of mesenchymal progenitor cells, and that the expression and activity of PDGF are important in wound healing and the like.

[4] Based on the descriptions in documents 1-8 cited in the international search report, the inventions of claims 1-8 lack an inventive step.

Documents 4 and 5 do not describe making PDGF into a transplant material, using a drug or transplant material containing PDGF in regenerative medicine for tissue and the like that has been damaged by rheumatoid arthritis, fracture, deficiency of periodontal and jaw bone, cerebral infarction, myocardial infarction or ischemia of the lower extremities, and administering that drug or transplantation material concurrently with, consecutively with, or separate from mesenchymal stem cells.

However, this authority finds that documents 1-3 describe the inclusion of PDGF in a transplantation material, and the use of PDGF together with bone marrow cells, including mesenchymal stem cells, and documents 6-8 state that mesencymal stem cells have the capability to differentiate into osteoblasts and cartilage cells, neurons, muscle cells, and the like, and that mesenchymal stem cells can be formed into a transplant material used in regenerative medicine and used for the treatment of bone diseases such as rheumatoid arthritis and the like, and diseases such as myocardial infarction and ischemia of the lower extremities.

This being the case, this authority finds that persons skilled in the art can easily conceive of making PDGF into a transplant material, using a drug or transplant material containing PDGF in regenerative medicine for tissue and the like that has been damaged by rheumatoid arthritis, fracture, deficiency of periodontal and jaw bone, cerebral infarction, myocardial infarction or ischemia of the lower extremities, and using the same together with mesenchymal stem cells.